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N-aminoacyl-azabicyclooctane carboxylic acid derivs. - useful as hypotensives, and their intermediates

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Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
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			DK 921144	A	19920917	
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Priority Applications (No Type Date): DE 3226768 A 19820717; DE 3143946 A 19811105

Cited Patents: 6.Jnl.Ref; DE 1955375; EP 37231; JP52039020; JP52116485; No-SR.Pub; 00 4.Jnl.

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EP 79022	B	G			
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US 5053519	A		9		
US 5061722	A		9		
JP 4217949	A		10	C07C-237/06	Div ex application JP 8690187
DK 9201144	A			C07D-209/52	Div ex application DK 824904
JP 93031544	B		6	C07D-209/52	Based on patent JP 58103364
DK 166624	B			C07K-005/06	Previous Publ. patent DK 8204904
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DK 172751	B			C07D-209/52	Previous Publ. patent DK 9201144
CZ 9104162	A3			C07D-209/52	

Abstract (Basic): EP 79022 A

Azabicyclooctane derivs. of formula (I) and their physiologically acceptable salts are new: (Hydrogen atoms at ring positions 1 and 5 are cis to each other and the 3-carboxy gp. has the endo orientation. R1 is H, allyl, vinyl or the side chain of an opt. protected naturally occurring alpha-amino acid. R2 is H, 1-6C alkyl, 2-6C alkenyl or aryl (1-4C alkyl). Y is H or hydroxy and Z is H, or Y and Z are together oxygen. X is 1-6C alkyl, 2-6C alkenyl, 5-9C cycloalkyl, 6-12C aryl (opt. substd. 1-3 times by 1-4C alkyl or alkoxy, hydroxy, halo, nitro, amino (opt. substd. by 1 or 2 1-4C alkyl), or methylenedioxy) or indol-3-yl).

Also new are the intermediates (IIIa) and (IIIb), and their salts,

(W is H, 1-6C alkyl or 7-8C aralkyl; W' is a gp. removable by hydrogenolysis, acid or base; and R2 is not benzyl or p-nitrobenzyl if W' is benzyl).

(I) have a strong and long-lasting hypotensive action (by inhibition of angiotensin-converting enzyme). Unit doses usually contain 1-100 mg.

Abstract (Equivalent): EP 79022 B

Azabicyclooctane derivs. of formula (I) and their physiologically acceptable salts are new: (Hydrogen atoms at ring positions 1 and 5 are cis to each other and the 3-carboxy gp. has the endo orientation. R1 is H, allyl, vinyl or the side chain of an opt. protected naturally occurring alpha-amino acid. R2 is H, 1-6C alkyl, 2-6C alkenyl or aryl (1-4C alkyl). Y is H or hydroxy and Z is H, or Y and Z are together oxygen. X is 1-6C alkyl, 2-6C alkenyl, 5-9C cycloalkyl, 6-12C aryl (opt. substd. 1-3 times by 1-4C alkyl or alkoxy, hydroxy, halo, nitro, amino (opt. substd. by 1 or 2 1-4C alkyl), or methylenedioxy) or indol-3-yl).

Also new are the intermediates (IIIa) and (IIIb), and their salts, (W is H, 1-6C alkyl or 7-8C aralkyl; W' is a gp. removable by hydrogenolysis, acid or base; and R2 is not benzyl or p-nitrobenzyl if W' is benzyl).

(I) have a strong and long-lasting hypotensive action (by inhibition of angiotensin-converting enzyme). Unit doses usually contain 1-100 mg. (37pp)

Abstract (Equivalent): US 5061722 A

Cis-endo-2-azabicyclo- (3.3.0)-octane-3-carboxylic acids of formula (I) and their salts are new. R2 = H, CH3, C2H5 or benzyl. The H atoms on the ring C atoms in the 1- and 5-posns. are in the cis configuration w.r.t. each other, the CO2H gp. on ring C atom in the 3-posn. is in the endo posn. w.r.t. the bicyclic ring system and the chirality centres all have the S-configuration.

N-(1-S-carboethoxy-3-phenyl-propyl)-S-alanyl-cis-endo-2-azabicyclo-(3.3.0)-octane-3-S-carboxylic acid is specifically claimed.

USE - As hypotensives (claimed).

US 5053519 A

A mixt. of enantiomers of cis-endo-2-azabicyclo (3.3.0) octane -3-carboxylic acid esters of formula (Ia) and (Ib) or their salts with acids or bases is new. In the formulae, W = H, 1-6C alkyl or 7-8C aralkyl. (Ia) and (Ib) may be prepared from cyclopentanone enamines of formula (II) and N-acylated beta-halo-alpha-amino carboxylic acid esters of formula (III). In (II) X1 = 2-10C dialkylamino or gp. (IV) where m and p = 1-3 and m+p = 3 or more and A = CH2, NH, O or S. In (III) X2 = a nucleofugic gp., e.g. Cl or Br, Y1 = 1-5C alkanoyl, 7-9C aroyl or another protective gp. customary in peptide chemistry which can be split off under acid conditions and R2 = 1-5C alkyl or 7-9C aralkyl.

USE - As intermediates for cis, endoazabicyclo (3.3.0) octane carboxylic acids useful as hypotensive agents. (9pp)c

US 4879403 A

A cpd. X-CO-CH2-C'H(COOR')-NH-C'H(R)-COOQ is produced by reacting an S-alpha-amino acid ester H2N-C'H(R)-COOQ with a keto-acrylic acid ester X-CO-CH=CH-COOR' to obtain a mixt contg mainly the desired cpd, isolating the desired cpd. by crystallisation and pref. removing Q by hydrogenolysis.

In the formulae the chiral centres C' have the S configuration; R is Me or 4-amino-butyl both opt. acylated; R' is 1-6C alkyl, pref. Me

or Et; X is R', 2-6C alkenyl, 5-9C cycloalkyl or 6-12C aryl all opt 1-3 times substd. by 1-4C alkyl or alkoxy or alkylamino, OH, halogen, NO2, NH2, di(1-4C) alkylamino and/or methylenedioxy or is indole-3-yl; Q is an esterifying gp removable by hydrogenolysis. X is esp Ph opt. 1-2 times substd. by F and/or Cl.

USE/ADVANTAGE - Used to control high blood pressure; the cpd. has a long lasting, intense hypotensive action and can be given orally or perenterally. (9pp),

US 4727160 A

New cis, endo-2-azabicyclo(3,3,0)-octane-3- carboxylic acid esters of formulae (IIIa) and (IIIb) and salts, can be made by new process comprising cyclising (X) to intermediate (XIa) and (XIb) and catalytic hydrogenation or redn. (X) are obtd. by reacting cyclopentanone enamine (VI), or radical (VII) and N-acylated beta-halogeno-alpha amino carboxylic acid esters (VIII). W is H, 1-6C alkyl, 7-8C aralkyl; Y is 1-5C alkanoyl, 7-9C aroyl; R2 is 1-5C alkyl, 7-9C aralkyl, X1 is 2-10C dialkylamino or (A) where m and o are each 1-3; (m + o) is 3; A is CH2, NH, O or S; X2 is Cl, Br or acrylic acid (B).

USE - Intermediate to cis, endoazabicyclo(3,3,0)-octane carboxylic acid of formula (I) by reacting (II) with (IIIa) or (IIIb). R1 is H, vinyl, allyl, or side chain of alpha amino acid R1-CH(NH2)COOH. Y is H or OH; Z is H, or Y and Z together are O; X is 1-6C alkyl, 2-6C alkenyl, 5-9C cycloalkyl 6-12C aryl, opt. substd. (I) are ACE-inhibitors used as long-lasting hypotensives at dosages eg. 13-1300 (13-400) mcg/kg/day p.o. Low toxicity. (9pp)

Title Terms: N; AMINO; ACYL; AZA; BI; CYCLOOCTANE; CARBOXYLIC; ACID; DERIVATIVE; USEFUL; HYPOTENSIVE; INTERMEDIATE

Derwent Class: B02

International Patent Class (Main): C07C-227/08; C07C-237/06; C07D-209/52; C07K-005/06

International Patent Class (Additional): A61K-031/40; A61K-031/405; A61K-037/02; C07C-099/00; C07C-101/28; C07C-103/52; C07C-227/10; C07C-227/14; C07C-227/16; C07C-229/28; C07C-229/36; C07D-029/02; C07D-317/48; C07D-317/60; C07D-403/12; C07D-405/12; C07D-451/04; C07K-001/02; C07K-005/12

File Segment: CPI

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Chemical Fragment Codes (M2):

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02 D012 D690 G010 G100 J0 J011 J111 J211 M210 M211 M212 M213 M214 M215 M216 M231 M232 M233 M272 M280 M281 M311 M312 M320 M321 M331 M332 M340 M342 M373 M391 M412 M511 M520 M530 M531 M540 M630 M640 M650 M710 M800 M903

03 D011 D019 D020 D021 D022 D140 D601 D699 F014 F521 G002 G010 G011 G012 G013 G014 G015 G016 G017 G019 G030 G040 G050 G100 G111 G112

G113 G553 G563 G573 G583 H1 H100 H101 H102 H103 H141 H142 H143 H181
H182 H341 H342 H343 H401 H402 H403 H404 H441 H442 H443 H444 H481
H498 H541 H542 H543 H600 H601 H602 H603 H608 H609 H641 H642 H643
H714 H721 H722 J0 J012 J013 J171 J172 J2 J271 J272 J371 J5 J581 L250
L432 M210 M211 M212 M213 M214 M215 M216 M231 M232 M233 M240 M262
M272 M273 M280 M281 M282 M283 M311 M312 M313 M314 M315 M321 M322
M331 M332 M333 M340 M342 M343 M344 M349 M371 M373 M381 M391 M392
M412 M413 M414 M415 M416 M510 M511 M512 M520 M521 M530 M531 M532
M533 M540 M541 M620 M710 M903

Ring Index Numbers: 00417; 00446; 00992